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(71) Applicant: INSITE VISION INCORPORATED [US/US]; 965 Atlantic Avenue, Alameda, CA 94501 (US).

(72) Inventors: BOWMAN, Lyle, M.; 5135 Mt. Tam Circle, Pleasanton, CA 94566 (US). PATEL, Rajesh; 2151 Vista Del Mar, San Mateo, CA 94404 (US). TSAO, Sheng-Wan; 37 Alley 648, Lane 102, Min-hu Road, Hsing-Chu, Taiwan 300 (CN). VO, Hoa, Vinh; 404 Coral Reef Road, Alameda, CA 94501 (US).

(74) Agents: FREED, Joel, M. et al.; Howrey & Simon, 1299 Pennsylvania Avenue, N.W., Washington, DC 20004-2402 (US).

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(54) Title: SUSPENSIONS FOR DELIVERY OF MEDICAMENT

(57) Abstract

Polymer medicament delivery systems containing an interactive agent which slows release of medicament out of the system for ophtalmic and dermal application.

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SUSPENSIONS FOR DELIVERY OF MEDICAMENT

FIELD OF THE INVENTION

This invention relates to new polymer medicament delivery systems containing an interactive agent which slows release of medicament out of the system. The invention may be used in ophthalmic or dermal formulations but is particularly useful as topical ophthalmic delivery systems for controlled, sustained release of medicaments after administration.

BACKGROUND OF THE INVENTION

In administration of medicaments to the eye and skin, a variety of factors can be important to successful therapy. The more important are: comfort, consistency and accuracy of dosage. When the product is being placed in the eye, the time of any vision interference, ease of administration, and timing of delivery are particularly important.

Conventional medicament delivery vehicles and particularly ophthalmic delivery systems, have suffered drawbacks in one or more of those areas. For example, eyedrops in the form of aqueous solutions or suspensions are rapidly washed away by the eye's tear fluid. Ointments or creams blur the vision, and also have comparatively short residence times in the eye. Gelatin lamellae or other films or sheets, ocular inserts and non-aqueous suspensions and emulsions all can cause immediate pain and continuing discomfort and can also interfere with vision.

A topical ophthalmic delivery system developed to overcome some of these problems is disclosed in WO 92/00044, Davis et al., published January 9, 1992. There, polymer medicament delivery systems are disclosed which are at a pH of from about 3.0 to about 6.5 when administered to the eye. Davis et al. teaches adjusting the pH from about 3.0 to about 6.5 and preferably from about 4.0 to about 6.0 using acceptable pH adjusting acids, bases or buffers. (Davis et al. at 13-14). The viscosity of the system increases in the eye as the pH of the system rises as a result of contact with tear fluid. The disclosed system may therefore be administered easily in drop form. After contact with the eye's tear fluid, the system rapidly gels to a greater viscosity than the viscosity of the administered drop.

Although systems disclosed in WO 92/00044 remain in the eye and release medicament over substantial periods of time, there is an ongoing need for further development of medicament delivery systems that release medication more slowly and more uniformly over time. Extensively crosslinking the polymers used as components of the delivery systems might be used to slow medicament release and inhibit polymer erosion but the crosslinking can undesirably limit the swellability of the system. Decreasing a system's swellability with crosslinking can result in particle formation that inhibits formation of a cohesive gel structure. There is therefore a particular need for systems that slowly release medicament yet remain swellable.

Conventional polymer based medicament delivery systems are made by dissolving polymers in a solvent, such as water, and then adjusting the pH to a desired level. The medicament may be added before or after adjusting the pH. When carboxyl-containing polymers are used, such as carboxyl vinyl polymer, the pH of the polymer dissolved in water is ordinarily around 3.0. The pH of the system is most commonly raised by the addition of base, such as sodium hydroxide. Addition of the base results in neutralization of some of the COOH groups on the polymer.

Applicants have found that addition of an interactive agent promotes under appropriate conditions, interactions between polymer particles, polymer chains and the interactive agent that, without reducing swellability slows the release of medicament contained in the system and improves resistance to erosion of the polymer system even in the presence of tear fluid.

Although the present invention is particularly useful for ophthalmic medicament delivery systems, it is not confined to that application. Medicament delivery systems of the present invention may be used, for instance, as formulations applied to the skin. A more detailed explanation of embodiments of the invention is set forth below.

SUMMARY OF THE INVENTION

In the present invention, an interactive agent forms associations with polymer molecules which slows the release of medicament out of the medicament delivery system relative to suspensions formulated without addition of an

interactive agent in accordance with the present invention. The associations are presently believed to result from ionic attractions between the interactive agent and the carboxy groups of the polymer. Hydrogen bonding may also occur between the agent and polymer and might, in some instances, contribute to the effects of the present invention. The associations resulting from use of the interactive agent promote formation of a stable matrix that inhibits movement of the medicament out of the delivery system.

One embodiment of the invention is a sustained release topical ophthalmic medicament delivery system comprising an aqueous suspension containing from about 0.1% to about 6.5% by weight, based on the total weight of the suspension, of a carboxyl-containing polymer and less than about 5% by weight of a cross-linking agent and an interactive agent. The pH of the suspension is sufficient to ionize at least about .5% of the polymer carboxyl groups and is sufficient to dissociate the interactive agent at least at two ionizable sites with one site being substantially ionized (dissociated). Under these circumstances, the interactive agent can form at least two interactions with different polymer chains.

The foregoing and other aspects of the present invention, as well as its nature, scope and utilization, will become more apparent to those skilled in the art from the following detailed description and the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides, in a preferred embodiment, an ophthalmic delivery system that may be administered in drop or ribbon form and that is swellable. Interactive agents that inhibit erosion of the system and slow release of medicament from the system are added to a solution of polymer. This procedure is particularly useful when phosphoric acid is the interactive agent. The invention may also be used for topical applications generally and dermal applications more specifically.

Interactive agents useful in the present invention are organic and inorganic acids having at least two active hydrogen groups available for dissociation (ionization). Such acids include boric, lactic, ortho-phosphoric acid, citric, oxalic, succinic, tartaric, and formic glycerophosphoric acids. Preferred acids are phosphoric and boric acids. The acid or base form of the interactive

agent may be used because when the desired pH of the final formulation is reached so that the dissociated species of the interactive agent will exist in solution. Accordingly, an interactive agent may be formed by addition of an appropriate salt, such as sodium borate, at conditions which result in the required dissociation.

Typically, when the polymer and water are first mixed together, the pH of the solution is about 3.0. In such conventional systems, the pH needs to be raised sufficiently so that at least about .5% of the polymer carboxyl groups are ionized and preferably about 20%. In addition, however, the pH must be sufficient to dissociate the interactive agent at least at two ionizable sites and the dissociation must be substantial at least at one site.

A substantial degree of dissociation occurs when at least one ionizable site of the agent has been about 20% dissociated (ionized) and the second site has experienced at least some degree of dissociation. Preferably the pH is adjusted to provide at least about 30% dissociation at one site, and more preferably dissociated about 50% ionization at one site. When dissociation has occurred to such an extent at one site, a smaller degree of dissociation at a second site (*i.e.*, 3-5% or 10%) may be sufficient for purposes of the invention. Obviously, if at least two or more sites are dissociated 20%, 30% or 50% or more, the objectives of the invention would also be provided. If the pH is lower than that necessary to provide a substantial degree of dissociation, the network of associations provided by the present invention does not occur or does not occur sufficiently to effectively provide slower release of drug.

Providing substantial dissociation is believed to be important because agents that have at least two sites at which dissociation (ionization) has occurred can form interactions with at least two polymer particles, polymer chains, or portions of polymer particles. It is formation of these interactions that is believed to create a matrix that is more difficult for drugs to migrate out of than matrixes not having an effective amount of interactive agent. Base required to increase the pH of the system may be added before or after the interactive agent is added to the polymeric suspension.

The pH at which the benefits of this invention are provided will, of course, depend on the pK of the ionizable sites on the agent. For ortho-

phosphoric acid, for instance, the benefits of the present invention are apparent at about pH 7.0 and above but not at about pH 5.0. When boric acid is used, sufficient dissociation also occurs at about pH 7 and above but not at about pH 5. For citric acid and EDTA, sufficient dissociation does occur at about pH 5 and above. The appropriate pH for any suitable acid can readily be determined by reference to standard tables which list the pK values and pH value at which different degrees of ionization occurs. An example of such a chart is in "The CRC Handbook of Chemistry and Physics", 67th Edition, (CRC Press, Inc., Boca Raton, Florida) at pages D159-D163. The disclosure of that publication is incorporated herein by reference.

The lightly cross-linked polymers of acrylic acid or the like used in practicing this invention are, in general, well known in the art. In a preferred embodiment, such polymers are prepared from at least about 90% and preferably from about 95% to about 99.9% by weight, based on the total weight of monomers present, of one or more carboxyl-containing monoethylenically unsaturated monomers. Acrylic acid is the preferred carboxyl-containing monoethylenically unsaturated monomer, but other unsaturated, polymerizable carboxyl-containing monomers, such as methacrylic acid, ethacrylic acid, ß-methylacrylic acid (crotonic acid), cis-α-methylcrotonic acid, trans-α-methylcrotonic acid, α-butylcrotonic acid, α-phenylacrylic acid, α-benzylacrylic acid, α-cyclohexylacrylic acid, ß-phenylacrylic acid (cinnamic acid), coumaric acid (o-hydroxycinnamic acid), unbellilc acid (p-hydroxycoumaric acid), can be used in addition to or instead of acrylic acid.

Such polymers are cross-linked by using a small percentage, i.e., less than about 5%, or from about 0.5% to about 5%, and preferably from about 0.5% to about 2.0%, based on the total weight of monomers present, of a polyfunctional cross-linking agent. Included among such cross-linking agents are non-polyalkenyl polyether difunctional cross-linking monomers such as divinyl glycol; 2,3-dihydroxyhexa-1,5-diene; 2,5-dimethyl-1,5-hexadiene; divinylbenzene; N,N-diallylacrylamide; N,N-diallylmethacrylamide and the like. Also included are polyalkenyl polyether cross-linking agents containing two or more alkenyl ether groupings per molecule, preferably alkenyl ether groupings containing terminal

$H_2C=C<$ groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an alkenyl halide such as allyl bromide or the like, e.g., polyallyl sucrose, polyallyl pentaerythritol, or the like; see, e.g., Brown, U.S. Patent No. 2,798,053. Diolefinic non-hydrophilic macromeric crosslinking agents having molecular weights of from about 400 to about 8,000, such as di- and poly- acrylates and methacrylates of diols and polyols, diisocyanate-hydroxyalkyl acrylate or methacrylate reaction products, and reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether dios or polysiloxane diols with hydroxyalkylmethacrylates, and the like, can also be used as the crosslinking agents; see, e.g. Mueller et al., U.S. Patents Nos. 4,192,827 and 4,136,250.

The lightly cross-linked polymers can, of course, be made from a carboxyl-containing monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a crosslinking agent or agents. They can also be polymers in which up to about 40%, and preferably from about 0% to about 20% by weight, of the carboxyl-containing monethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomers containing only physiologically innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethylhexylacrylate, octyl methacrylate, 2-hydroxethyl-methacrylate, 3- hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, and the like; see Mueller et al., U.S. Patent No. 4,548,990 for a more extensive listing of such additional monoethylenically unsaturated monomers. Particularly preferred polymers are lightly cross-linked acrylic acid polymers wherein the crosslinking monomer is 2,3-dihydroxyhexa-1,5-diene or 2,3-dimethylhexa-1,5-diene.

Lightly cross-linked polymers useful in practicing this invention are preferably prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 50 μm in equivalent spherical diameter; e.g., to provide dry polymer particles ranging in size from about 1 to about 30 μm, and preferably from about 3 to about 20 μm, in equivalent spherical diameter. In general, such

polymers will range in molecular weight estimated to be about 250,000 to about 4,000,000, and preferably greater than 2,000,000.

For ophthalmic applications, aqueous suspensions containing polymer particles prepared by suspension or emulsion polymerization whose average dry particle size is appreciably larger than about 50 μm in equivalent spherical diameter are less comfortable when administered to the eye than suspensions otherwise identical in composition containing polymer particles whose equivalent spherical diameters are, on the average, below about 50 μm. Moreover, lightly cross-linked polymers of acrylic acid or the like prepared to a dry particle size appreciable larger than about 50 μm in equivalent spherical diameter and then reduced in size, e.g., by mechanically milling or grinding, to a dry particle size of not more than about 50 μm in equivalent spherical diameter do not work as well as polymers made from aqueous suspensions. This may occur because mechanical milling or grinding provides particles that are not as uniform or that have a wider particle size distribution. In any event, such mechanically reduced particles are less easily hydratable in aqueous suspension than particles prepared to the appropriate size by suspension or emulsion polymerization, and up to about 40% by weight, e.g., from about 0% to about 20% by weight, based on the total weight of lightly cross-linked particles present, of such milled or ground polymer particles can be admixed with solution or emulsion polymerized polymer particles having dry particle diameters of not more than about 50 μm.

Ophthalmic suspensions of the present invention may be formulated so that they retain the same or substantially the same viscosity in the eye that they had prior to administration to the eye. Alternatively, ophthalmic suspensions of the present invention may be formulated so that the viscosity of the suspension increases from increased gelation upon contact with tear fluid. When this increase in gelation is desired, teachings of WO 92/00044, published January 9, 1992 are preferably followed.

The particles preferably have a narrow particle size distribution within a 10 μm band of major particle size distribution which contains at least 80%, more preferably at least 90%, most preferably at least 95% of the particles.

Also, there is no more than 20%, preferably no more than 10%, and most preferably no more than 5% particles are fines, *i.e.*, of a size below 1 μm.

It is also generally preferred that as the average particle size is lowered from the upper limit of 50μm, more preferably 30μm, to lower sizes such as 6μm, that the band of major particle size distribution be also narrowed, for example to 5μm. Preferred sizes for particles within the band of major particle distribution are less than about 30μm, more preferably less than about 20μm, most preferably from about 1μm to about 5μm. The use of a monodispersion of particles will give maximum viscosity and an increased eye residence time of the ophthalmic medicament delivery systems for a given particle size. Monodisperse particles having a particle size of 30 μm and below are most preferred. Good particle packing is aided by a narrow particle size distribution.

The aqueous suspensions of this invention will contain amounts of lightly cross-linked polymer particles ranging from about 0.1% to about 6.5% by weight, and preferably from about 0.5% to about 4.5% by weight, based on the total weight of the aqueous suspension. They will preferably be prepared using pure, sterile water, preferably deionized or distilled, having no physiologically or ophthalmologically harmful constituents, and will be adjusted, after addition of interactive agent, to a pH of from about 3.0 to about 9.0 and preferably from about 6.5 to about 7.5. Because systems of the present invention are ordinarily acidic when the interactive agent is added, ph is adjusted with acceptable pH adjusting bases or buffers. It is possible, however, to adjust the pH using any physiologically and ophthalmologically acceptable pH adjusting acids, bases or buffers. Such acids may include acetic, boric, citric, lactic, ortho-phosphoric, hydrochloric, or the like. Bases used to adjust the pH of the system include sodium hydroxide, sodium phosphate, ammonium hydroxide, sodium borate, sodium citrate, sodium acetate, sodium lactate, THAM (trishydroxymethylamino-methane), or the like. Salts and buffers that may be used as agents include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases. Because the pH of conventional polymer suspensions is low (about 3.0) base will typically be the only pH adjusting agent added.

When formulating the aqueous suspensions of this invention, their osmotic pressure (π) will be adjusted to from about 10 milliosmolar (mOsm) to about 400 mOsm, and preferably from about 200 to about 300 mOsm, using appropriate amounts of physiologically and ophthalmologically acceptable salts. Sodium chloride is preferred to approximate physiologic fluid, and amounts of sodium chloride ranging from about 0.01% to about 1% by weight, and preferably from about 0.05% to about 6.0% by weight, preferably about 0.05% to about 2% by weight, based on the total weight of the aqueous suspension, will give osmolalities within the above-stated ranges. Equivalent amounts of one or more salts made up of cations such as potassium, sodium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfite and the like, e.g., potassium chloride, sodium thiosulfate, sodium bisulfite, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated ranges. Polyols may be added to adjust osmolarity.

The amounts of lightly cross-linked polymer particles, the pH, and the osmotic pressure chosen from within the above-stated ranges will be correlated with each other and with the degree of crosslinking to give aqueous suspensions having viscosities ranging from about 1,000 to about 30,000 centipoise, and preferably from about 5,000 to about 20,000 centipoise, as measured at room temperature (about 25°C) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm.

A viscosity of about 30,000 cps to about 100,000 cps is preferred for administration to the eye as a ribbon. The medicaments contained in these drug delivery systems will be released at rates that depend on such factors as the drug itself and its physical form, the extent of drug loading and the pH of the system, as well as on any drug delivery adjuvants, such as ion exchange resins compatible with the ocular surface, which may also be present.

Medicaments are substances used in treating or ameliorating a disease or medical condition. For dermal applications, these include drugs that penetrate the skin to treat conditions of the body (transdermal) and drugs that are applied to the skin to treat conditions specifically of the skin or dermal layers.

They also include drugs intended to treat therapeutically conditions of the eye itself or the tissues surrounding the eye and drugs administered via the ophthalmic route to treat therapeutically a local condition other than one involving the eye. The ophthalmic medicaments will typically be incorporated in the topical delivery systems of this invention in therapeutically active amounts comparable to amounts administered in other dosage forms, usually in amounts ranging from about 0.005% to about 10% by weight, and preferably from about 0.01% to about 5% by weight, based on the total weight of the formulation. Thus, for example, from about 0.01% to about 1% by weight of the anti-inflammatory steroid fluorometholone can be administered to the eye in this manner.

Medicaments useful for dermal application to the skin include bupiracaine HCl, tetracaine HCl, benzocaine, cocaine HCl, dibucaine, dyclinine HCl, lidocaine, pramoxine HCl, proparacaine HCl, benoxinate HCl, benzyl alcohol, butacaine, gentamicin sulfate, neomycin sulfate, erythromycin, sulfacetamide sodium, silver sulfadiazine, hydrocortisone, beclomethasone dipropionate, flurandrenolide, triamcinolone acetonide, benzoyl peroxide, fluorouracil, cetylpyridinium chloride, cloflucarban, triclosan, triclocarban and t-retinoic acid. These or other drugs may treat topical conditions of the skin, dermal conditions within the skin, or systemic conditions of the person on whom the medicament is applied.

Suspensions of the present invention can be applied to the skin directly as an aqueous suspension or as an ointment or cream or as a component of an oil. When an aqueous suspension is formulated for use in dermal applications the polymer content of the suspension may range from about .1% to about 20% but is preferably about 1% to about 10%. The pH of dermal formulations and of suspension is preferably about 5 to about 9 and more preferably about 6.5 to about 7.5. Formulating suspensions of the present invention into creams, ointments or oils for dermal application is within the skill of those who ordinarily prepare formulations for dermal use. To administer medicaments to the skin, aqueous suspensions of the present invention may be administered directly to the skin or as a component of an ointment, cream or oil. Medicaments administered to the skin with the present invention may treat conditions of the skin surface, of the dermal

layers or conditions of the body. To treat conditions of the body with dermal application of the present invention, of course, it will be necessary for the drug to be one which penetrates the skin.

An illustrative but by no means exhaustive listing of such medicaments for ophthalmic use includes demulcents (for relief of "dry eye"), antibiotics, antivirals, steroids, amino-substituted steroids, anti-inflammatory agents, peptides, polypeptides, cardiotonics, antihypertensives, antiallergics, alpha- and betaadrenergic blocking agents, ophthalmic medicaments such as anticataract agents, antiglaucoma agents and ophthalmic antiinflammatory agents, ophthalmic lubricating agents, ophthalmic topical or regional anesthetic agents, etc. Specific medicaments that can be used in the present invention include drugs such as pilocarpine, idoxuridine, carbachol, bethanechol, timolol, atenolol, labetolol, metroprolol, nadolol, oxprenolol, pindolol, sotalol, betaxolol, acebutolol, alprenolol, levo-bunolol, p-aminoclonidine, dipivefrin, tetracycline, epinephrine, phenylephrine, eserine, phospholine, aceclidine, demecarium, cyclopentolate, homatropine, scopolamine, nitroglycerine, ethacrynic acid, furosemide, amiloride, chlortetracycline, bacitracin, neomycin, polymyxin, polymyxin B, gramicidin, oxytetracycline, chloramphenicol, gentamicin, penicillins, erythromycin, sulfacetamide, tobramycin, trospectomycin, vancomycin, ciprofloxacin, perfloxacin, olflaxacin, enoxacin, naphazoline hydrochloride, clindamycin, isoflurophate, fluorometholone, dexamethasone, hydrocortisone, fluorocinolone, medrysone, prednisolone acetate, methylprednisolone, fluticasone propionate, betamethasone, triamcinolone, estradiol, ibuprofen, flurbiprofen, naproxen, esters of ibuprofen, flurbiprofen, and naproxen; ketorolac, suprofen, interferons, cromolyn, gancyclovir, aminozolamide, all trans-retinoic acid (Vitamin A) and the nontoxic, pharmaceutically acceptable salts thereof. Pro-drug counterparts are also within the scope of the present invention. Ophthalmic lubricating agents are materials capable of inducing natural lacrimation or creating artificial lacrimation and include, for example, polyvinylalcohol, cellulose polymers such as hydroxypropyl methyl cellulose, polylactams such as polyvinylpyrrolidone and the like. "Dry eye" formulations that comprise pure water and a lightly cross-linked polymer of the type described hereinabove in an amount within the range also set

forth hereinabove, hypotonic in saline and thus having the requisite osmotic pressure are also contemplated as being within the scope of this invention. Topical or regional anesthetic agents include ones used during ophthalmic surgery or other ophthalmic procedures, such as lidocaine, cocaine, benoxinate, dibucaine, proparacaine, tetracaine, etidocaine, procaine, hexylcaine, bupivacaine, mepivacaine, prilocaine, chloroprocaine, and the like.

The term "pharmaceutically acceptable salt" refers to those salts of the parent compound that do not significantly or adversely affect the pharmaceutical properties (e.g., toxicity, efficacy, etc.) of the parent compound. Pharmaceutically acceptable salts administrable by means of the aqueous suspensions of this invention include, for example, chloride, iodide, bromide, hydrochloride, acetate, nitrate, stearate, pamoate, phosphate and sulfate salts. It is sometimes desirable to use an appropriate salt form of the medicament that increases the water solubility or polar characteristics of the free drug.

A number of variations in formulation techniques may be used with the present invention. For example, the drug, the lightly cross-linked polymer particles, and the osmolality-adjusting salt can be preblended in dry form, added to all or part of the water, and stirred vigorously until apparent polymer dispersion is complete, as evidenced by the absence of visible polymer aggregates. An interactive agent or combination of such agents may then be added in an amount sufficient to promote interactions between polymer particles and the agent to increase viscosity of the solution. Sufficient pH adjusting agent may then be added incrementally to reach the desired pH, and more water to reach 100 percent formula weight can be added at this time, if necessary. Another convenient method involves adding the drug to about 95 percent of the final water volume and stirring for a sufficient time to saturate the solution.

Solution saturation can be determined in a known manner, e.g., using a spectrophotometer. The lightly cross-linked polymer particles and the osmolality-adjusting salt are first blended in dry form and then added to the drug--saturated suspension and stirred until apparent polymer hydration is complete. Following the incremental addition of sufficient pH adjusting agent to reach the

desired pH, the remainder of the water is added, with stirring, to bring the suspension to 100 percent formula weight.

The aqueous suspensions can be packaged in preservative-free, single-dose non-reclosable containers. This permits a single dose of the medicament to be delivered to the eye one drop at a time, with the container then being discarded after use. Such containers eliminate the potential for preservative-related irritation and sensitization of the corneal epithelium, as has been observed to occur particularly from ophthalmic medicaments containing mercurial preservatives. Multiple-dose containers can also be used, if desired, particularly since the relatively low viscosities of the aqueous suspensions of this invention permit constant, accurate dosages to be administered dropwise to the eye as many times each day as necessary. In those suspensions where preservatives are to be included, suitable preservatives are chlorobutanol, polyquat, benzalkonium chloride, cetyl bromide, and the like.

Other additives may be placed in the system to further slow release of drug. Addition of ion exchange resin, for instance, slows release of the drug by forming ionic bonds to the medicament. The ionic and non-ionic attractive force between the drug and the larger resin molecule is believed to slow migration of the drug out of the system. A viscosity increasing agent, such as a polysaccharide gel (*i.e.* Gelrite), slows release of the drug by making the polymer medium more difficult for the drug to migrate through.

In order that those skilled in the art can more fully appreciate aspects of this invention, the following examples are set forth. These examples are given solely for purposes of illustration, and should not be considered as expressing limitations unless so set forth in the appended claims.

EXAMPLE 1

Noveon AA-1 is slowly dispersed into a beaker containing approximately 2/3 of the final weight of water and stirred for 1.5 hours. EDTA, o-phosphoric acid (an interactive agent) and sodium borate (an interactive agent) are added sequentially and mixed for 10 minutes after each addition. The combination of interactive agents is added while the dissolved polymer is at a pH of about 3.0-3.5. The mixture is sterilized by autoclaving at 121°C for 20

minutes. Apraclonidine, a medicament useful in treatment of glaucoma, is dissolved separately in approximately 1/5 of the final weight of water and added to the polymer mixture by sterile filtration. The mixture is adjusted to pH 6 with 10N NaOH, brought to final weight with water by sterile filtration and aseptically filled into unit-dose containers.

EXAMPLE 2

Noveon AA-1 is slowly dispersed into a beaker containing approximately 2/3 of the final weight of water and stirred for 1.5 hours with an overhead stirrer. A combination of EDTA, o-phosphoric acid (an interactive agent) and sodium borate (an interactive agent) are added sequentially and mixed 10 minutes after each addition. The o-phosphoric acid is added while the polymer-containing solution is at a pH of about 3.0-3.5. The Amberlite IRP is added to the solution and stirred until it is uniformly mixed without any lumps (approximately 15 minutes). The mixture is sterilized by autoclaving at 121°C for 20 minutes. Apraclonidine is dissolved separately in approximately 1/5 of the final weight of water, and is then added to the polymer mixture by sterile filtration and stirred at least 12 hours to ensure that the apraclonidine is ionically bound to the Amberlite. The mixture is adjusted to pH 7 with 10N NaOH, brought to final weight with water by sterile filtration and aseptically filled into unit-dose containers.

The formulations of Examples 1 and 2 are summarized in the following Table I.

TABLE I

Ingredients	Example 1 (% w/w)	Example 2 (% w/w)
APRACLONIDINE HCl	1.15	1.15
NOVEON AA-1	1.3	1.3
EDTA	0.1	0.1
o-PHOSPHORIC ACID	0.5	0.25
SODIUM BORATE	0.5	0.25
AMBERLITE IRP		2
NaOH	q.s. to pH	q.s. to pH
PURIFIED WATER	q.s. to 100	q.s. to 100
pH	6.0	7.0

Examples 3-6

Formulations 3, 4, 5 and 6 appearing in Table II below, are prepared by slowly dispersing Noveon AA-1 into a beaker containing approximately 2/3 of the final weight of water and stirred for 1.5 hrs. with an overhead stirrer. Edetate disodium, and sodium chloride (Formulations 5 and 6) or o-phosphoric acid and sodium borate (Formulations 3 and 4) are then added sequentially and mixed for 15 minutes after each addition while the polymer solution is at a pH of about 3.0-3.5. The mixture is sterilized by autoclaving at 121°C for 20 minutes and then allowed to cool down to room temperature before proceeding with the next steps. Levobunolol HCl, a medicament for ophthalmic uses, is dissolved separately in approximate 1/10 of the final weight of water. The levobunolol HCl solution is then added to the polymer solution by sterile filtration (0.2 μm) and mixed well for 15 minutes. The mixture is adjusted to pH 5.4 (Formulation 3 and 5) and 7.5 (Formulation 4 and 6) with 10N sodium hydroxide/6N hydrochloric acid, and brought to final weight with remaining water by aseptic sterile filtration.

The addition of the interactive agents o-phosphoric acid and sodium borate, decreased the release rate of the drug, thereby extend the duration of release of levobunolol HCl over time. The improvement is more significant at pH 7.5 than at pH 5.4.

The release rates are charted in accordance with the following procedure. Diffusion cells are made of plexiglass with a flow through design. An elution fluid (phosphate buffered saline at pH 7.4) is maintained at 37°C and pumped at about 7.4 milliliters per hour through the diffusion cell and into a UV-Vis Diode Array Spectrophotometers (model 8452A, Hewlett Packard, Sunnyvale, CA.) About 25 mg test material is injected into the sample port and the drug concentration is monitored at the λ max of the drug being studied.

TABLE II

INGREDIENTS	Example 3 (% w/w)	Example 4 (% w/w)	Example 5 (% w/w)	Example 6 (% w/w)
Noveon AA-1	1.3	1.3	1.3	1.3
Disodium Edetate	0.1	0.1	0.1	0.1
Sodium Chloride	---	---	0.44	0.44
O-Phosphoric Acid	0.5	0.5	---	---
Sodium Borate	0.5	0.5	---	---
Levobunolol HCl	0.25	0.25	0.25	0.25
Purified Water	q.s. 100%	q.s. 100%	q.s. 100%	q.s. 100%
pH	5.4	7.5	5.4	7.5

The release rates for the foregoing formulations, if measured about 15 minutes after injection into the sample port, are: Formulation 3, about 160 µg/hr.; Formulation 4, about 50 µg/hr; Formulation 5, about 150 µg/hr, and Formulation 6 about 130 µg/hr. In each instance, the measurement taken at about 15 minutes is the highest release rate value for each formulation. The release rate of all of the formulations approaches zero between about 2 1/2 hours and 3 hours. Comparing the release rates of Formulations 3 and 4 indicates that the phosphoric acid interactive agent does not significantly inhibit drug release at a pH of 5.4 but it does in the formulation having a pH of 7.5. Comparing the release rates for

formulations 4 and 6 shows that the formulation containing interactive acid agent at pH 7.5 shows release of drug to a significantly greater extent than a formulation without interactive agent.

Example 7-10

Formulations 7, 8, 9 and 10 appearing in Table III below, are prepared by slowly dispersing Noveon AA-1 into a beaker containing approximately 2/3 of the final weight of water and stirred for 1.5 hours with an overhead stirrer. Edetate disodium, and sodium chloride (Formulations 7 and 8) or ortho-phosphoric acid and sodium borate, (Formulations 9 and 10) are then added sequentially and mixed for 15 minutes after each addition while the polymer solution is at a pH of about 3.0-3.5. The mixture is sterilized by autoclaving at 121°C for 20 minutes and then allowed to cool down to room temperature before proceeding with the next steps. Proparacaine HCl, a medicament for ophthalmic uses, is dissolved separately in approximate 1/10 of the final weight of water. The Proparacaine HCl solution is then added to the polymer solution by sterile filtration (0.2 μm) and mixed well for 15 minutes. The mixture is adjusted to about pH 5.4 (Formulation 7 and 9) and about 7.4 or 7.5 (Formulation 8 and 10) with 10N sodium hydroxide/6N hydrochloric acid, and brought to final weight with remaining water by aseptic sterile filtration. Formulation 10 illustrates the invention.

TABLE III

Ingredients	Example 7 (% w/w)	Example 8 (% w/w)	Example 9 (% w/w)	Example 10 (% w/w)
Noveon AA-1	1.3	1.3	1.3	1.3
Disodium Edetate	0.1	0.1	0.1	0.1
Sodium Chloride	0.27	0.27	--	--
O-Phosphoric Acid	--	--	0.5	0.5
Sodium Borate	--	--	0.5	0.5
Proparacaine HCl	0.5	0.5	0.5	0.5
pH	5.4	7.5	5.4	7.4
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%	q.s. to 100%

Formulations 11, 12 and 13 further illustrate the invention and are set forth in Table IV below. Their preparation is described in the following Examples 11, 12 and 13.

Example 11

To make Formation 11, Noveon AA-1 is slowly dispersed into a beaker containing approximately 2/3 of the final weight of water and stirring for 1.5 hrs. with an overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate disodium acid (EDTA) and citric acid (an interactive acid agent) are then added to the solution and stirred for 10 minutes. The polymer solution is at a pH of about 3.0-3.5. Then Amberlite IRP is added to the solution and stirred until it is uniformly mixed without any lumps (approximately 15 minutes). Amberlite IRP is an ion exchange resin available from Rhom & Haas which is believed to form ionic bonds with the drug. The mixture is sterilized by autoclaving at 121°C for 20 minutes. Apraclonidine, medicament frequently used in the treatment of glaucoma, is dissolved separately in approximately 1/5 of the final weight of water, added to the polymer mixture by sterile filtration and stirred at least 12 hours to ensure that the apraclonidine is

bound to the Amberlite. The mixture is adjusted to pH 4.5 with 10N sodium hydroxide, brought to the final weight with water by sterile filtration and aseptically filled into unit-dose containers.

Example 12

To make Formulation 12, Noveon AA-1 is slowly dispersed into a beaker containing approximately 3/4 of the final weight of water and stirred for 1.5 hrs. with an overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate disodium acid (EDTA) and citric acid (an interactive acid agent) are then added to the solution and stirred for 10 minutes after each addition. The polymer solution is at a pH of about 3.0-3.5. The mixture is adjusted to pH 4.5 with 10N NaOH and the weight is adjusted to the difference between the final weight minus the weight of Gelrite to be added. The mixture is heated to 75°C and the Gelrite is added. Gelrite is a polysaccharide available from Schweizer Hall used to increase viscosity of the suspension. The temperature is increased to 90°C and the mixture is stirred for a half-hour. The mixture is then sterilized by autoclaving at 121°C for 20 minutes. MK 417, a drug useful in treatment of glaucoma, is then dissolved in 1/5 of the final weight of water and sterile filtered into the mixture and stirred for 15 minutes. MK 417 is a carbonic anhydrase inhibitor available from Merck. The pH is adjusted to 6.0 with sodium hydroxide. The final weight is made up with sterile filtered water and the product is aseptically filled into unit-dose containers.

Example 13

To make Formulation 13, Noveon AA-1 is slowly dispersed into a beaker containing approximately 2/3 of the final weight of ethanol/water mixture and stirred for 1.5 hrs. with an overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate disodium acid (EDTA), o-phosphoric acid (an interactive agent) and sodium borate (an interactive agent) are then added to the solution and stirred for 10 minutes after each addition. The polymer solution is at a pH of about 3.0-3.5. t-Retinoic acid, medicament frequently used in the treatment of acne, is dissolved separately in approximately 1/5 of the final weight of ethanol/water mixture added to the polymer mixture and

stirred for 15 minutes. The mixture is adjusted to an apparent pH 7 with 10N sodium hydroxide, brought to final weight with ethanol/water mixture.

TABLE IV

Ingredients	Example 11 (% w/w)	Example 12 (% w/w)	Example 13 (% w/w)
Noveon AA-1	1.3	1.3	2.0
EDTA	0.1	0.1	0.1
o-Phosphoric Acid	---	---	0.5
Citric Acid	0.5	0.5	---
Sodium Borate	---	---	0.5
Ethanol	---	---	90.0
Amberlite	5.0	---	---
Gelrite	---	0.3	---
MK 417 HCl	---	2.0	---
Apraclonidine HCl	1.15	---	---
t-Retinoic Acid	---	---	0.1
Sodium Hydroxide	q.s. to pH 4.5	q.s. to pH 6.0	q.s. to pH 7.0
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%

The above discussion of this invention is directed primarily to preferred embodiments and practices thereof. It will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts described herein can easily be made with departing from the spirit and scope of the invention as defined by the following claims.

We Claim:

1. A sustained release topical ophthalmic medicament delivery system comprising:

an aqueous suspension from about 0.1% to about 6.5% by weight, based on the total weight of the suspension, of a carboxyl-containing polymer and less than about 5% by weight of a cross-linking agent;

an interactive agent having at least two ionizable sites where dissociation can occur; and

wherein the pH of the suspension is sufficient to ionize at least about .5% of the polymer carboxyl groups and is sufficient to substantially dissociate the interactive agent at least at two ionizable sites, with one site being substantially disassociated and wherein the interactive agent forms at least two associations with the polymer.

2. A sustained release topical ophthalmic medicament delivery system as recited in claim 1 wherein at least one ionizable site of the interactive agent is at least 20% dissociated.

3. A sustained release topical ophthalmic medicament delivery system as recited in claim 1 wherein at least one ionizable site of the interactive agent is at least 30% dissociated.

4. A sustained release topical ophthalmic medicament delivery system as recited in claim 1 wherein at least one ionizable site of the interactive agent is at least 50% dissociated.

5. A sustained release topical system as recited in claim 3 wherein said interactive agent is selected from the group consisting of o-phosphoric acid, boric acid, and lactic acid.

6. A sustained release topical ophthalmic medicament delivery system as recited in claim 5 acid wherein the interactive agent makes up about 1% or less of the weight of the system.

7. A sustained release topical ophthalmic medicament delivery system as recited in claim 1 and further comprising an ion exchange resin.

8. A sustained release topical ophthalmic medicament delivery system as recited in claim 1 and further comprising a polysaccharide gel, added to increase the viscosity of the system.

9. A sustained release topical ophthalmic delivery system as recited in claim 3 wherein the suspension has a viscosity of from about 1,000 to about 30,000 centipoises and is administrable in drop form.

10. A sustained release topical ophthalmic delivery system as recited in claim 3 wherein the suspension has a viscosity of from about 30,000 centipoises to about 100,000 centipoises and is administrable in ribbon form.

11. A sustained release topical ophthalmic medicament delivery system as recited in claim 8 wherein the suspension has a pH of about 6.5 to about 7.5, and an osmotic pressure of from about 10 to about 400 mOsm;

the polymer has average particle size of not more than about 50 μm in equivalent spherical diameter and is lightly cross-linked; and

wherein the polymer is a monodispersion of particles wherein at least about 80% of the particles are within a no more than about 10 μm band of major particle size distribution and no more than about 20% of the total particles are fines.

12. A sustained release topical ophthalmic medicament delivery system as recited in claim 8 wherein the interactive agent is o-phosphoric acid or boric acid or a combination thereof.

13. A sustained release topical ophthalmic medicament delivery system as recited in claim 9 wherein the interactive agent is o-phosphoric acid or boric acid or a combination thereof.

14. A method of preparing a sustained release topical ophthalmic delivery system comprising:

preparing an aqueous suspension of a carboxyl-containing polymer prepared by polymerizing one or more carboxyl-containing monoethylenically unsaturated monomers and less than about 5% by weight of a cross-linking agent,

wherein the suspension contains from about 0.1% to about 6.5% by weight, based on the total weight of the system, of polymer formed from said monomers and less than about 5% by weight, of the cross-linking agent; and

mixing an interactive agent with said aqueous suspension of polymer, and adjusting the pH of the system to provide a pH sufficient to ionize at least about .5% of the polymer carboxyl groups and that is sufficient to dissociate the interactive agent at least at two ionizable sites, with one site being substantially dissociated, and wherein the agent forms at least two associations with the polymer.

15. A sustained topical medicament delivery system for dermal applications in the form of an ointment, cream or oil comprising:

an aqueous suspension of from about 0.1% to about 6.5% by weight, based on the total weight of the suspensions, of a carboxyl-containing polymer and less than about 5% by weight of a cross-linking agent;

an interactive acid agent having at least two ionizable sites where dissociation can occur; and

wherein the pH of the suspension is sufficient to ionize at least about .5% of the polymer carboxyl groups and is sufficient to dissociate the interactive agent at least at two ionizable sites, with one site being substantially dissociated, and wherein the interactive agent forms at least two associations with the polymer.

16. A sustained topical medicament delivery system as recited in claim 15 wherein the polymer content of the aqueous suspension is from about .1% to about 20% and the pH of the suspension is about 5.0 to about 9.0.

17. A method of delivering medicament to the skin comprising:

preparing an aqueous suspension of a carboxyl-containing polymer prepared by polymerizing one or more carboxyl-containing monoethylenically unsaturated monomers and less than about 5% by weight of a cross-linking agent, wherein the suspension contains from about 0.1% to about 6.5% by weight, based on the total weight of the system, of polymer formed from said monomers and less than about 5% by weight of the cross-linking agent; and

mixing an interactive agent having at least two ionizable sites where dissociation can occur with said aqueous suspension of polymer, and adjusting the pH of the system to provide a pH sufficient to ionize at least about .5% of the polymer carboxyl groups and is sufficient to dissociate the interactive agent at least at two ionizable sites, with one site being substantially dissociated, and wherein the agent forms at least two associations with the polymer; and

administering said suspension to the skin.

18. A sustained topical medicament delivery system for topical applications comprising:

an aqueous suspension of from about 0.1% to about 6.5% by weight, based on the total weight of the suspensions, of a carboxyl-containing polymer and less than about 5% by weight of a cross-linking agent;

an interactive agent having at least two ionizable sites where dissociation can occur; and

wherein the pH of the suspension is sufficient to ionize at least about .5% of the polymer carboxyl groups and is sufficient to dissociate the interactive agent at least at two ionizable sites, with one site being substantially dissociated, and wherein the interactive agent forms at least two associations with the polymer.

INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/US 94/08331

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00 A61K47/32 A61K47/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP,A,0 472 327 (SENJU PHARMACEUTICAL CO. LTD.) 26 February 1992 see claims 1,5,7,8,13 see page 3, line 1 - line 52	1-6,9, 10,13-18
Y	PATENT ABSTRACTS OF JAPAN vol. 016, no. 289 (C-0956) 26 June 1992 & JP,A,04 077 434 (KANJI TAKADA) 11 March 1992 see abstract	1-6,9, 10,13-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ventura Amat, A

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